REMARKS

Claims 41-49 are pending in the present application. Claims 41-49 have been canceled and claims 50-63 have been added. Support for the amendments can be found throughout the specification and claims as originally filed. For example, support may be found at, pages 56 and 57, beginning on line 22 of page 56. No new matter has been added by virtue of the amendments.

Claim Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 41-49 were rejected under 35 U.S.C. 112, second paragraph, as "being incomplete for omitting essential steps, such omission amounting to a gap between steps." Specifically, the Examiner asserts that the step that correlates cellular growth or proliferation with the determination of a test compound capable of treating cellular growth, proliferation or cancer is omitted.

Applicants respectfully traverse this rejection. Applicants have canceled claims 41-49 and added claims 50-51 which recite, "determining **whether the test compound ameliorates** cellular growth or proliferation of the cancer cells; thereby identifying a candidate compound capable of treating a cellular growth or proliferation disorder..." The amendments contained herein are believed to obviate the rejection. Thus, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection.

Claim Rejections Under 35 U.S.C. §112, First Paragraph

Claims 41-49 were rejected under 35 U.S.C. 112, second paragraph, as "failing to comply with the enablement requirement." The Examiner argues that undue experimentation would be required to practice the invention. The Examiner provided four arguments for finding that the claims are not enabled: 1) the specification does not provide a repeatable method for obtaining the biological material; 2) the art of anticancer drug discovery is "highly unpredictable"; 3) protein chemistry is "unpredictable in the current state of the art"; and 4) knowing the structural nature of the SEQ ID NO:2 substrate is also necessary to practice the invention.

Applicants respectfully traverse this rejection. As explained in greater detail below, applicants disagree with the Examiner's conclusions based on the arguments set forth.

First, the Examiner asserts that claims are not enabled because of missing ATCC deposit information in the specification. Applicants respectfully draw the Examiner's attention to the Preliminary Amendment filed on August 7, 2003, in which the specification has been amended to include the omitted reference to ATCC deposit information for the molecules of the invention. A copy of the Preliminary Amendment and the stamped returned postcard is submitted herewith for the Examiner's convenience. Additionally, a Statement of Biological Culture Deposit in accordance with the Budapest Treaty and 37 C.F.R. §1.801-1.809 and a copy of the Deposit Receipt are being filed concurrently herewith.

Second, the Examiner asserts that the claims are not enabled because "the art of anticancer drug discovery for cancer therapy is unpredictable. According to the Examiner, because of this unpredictability, "in the absence of experimental evidence, one skilled in the art would not accept that going through the active steps of the instant claims would successfully lead to identifying a compound capable of treating cancer."

Applicants respectfully disagree and submit that the claimed subject matter is fully enabled. Despite the problems discussed by Gura (*Science* 278:1041-2, 1997), Jain (*Sci. Am.* 271:58-65, 1994) and the other references cited by the Examiner, the presently claimed methods are but one aspect in the whole of the drug discovery process. Despite the fact that few compounds identified in screens ultimately prove to be a successful therapy, for various reasons, large pharmaceutical companies, small start-up companies, and government and academic researchers the world over spend countless hours and many, many millions of dollars using *in vitro* target-based screens to identify candidate therapeutic agents for the treatment of cancer. Researchers are well aware of the various challenges of the drug discovery process noted by the Examiner. However, they continue to use target-based screening because they believe that such screens are useful for identifying candidate therapeutic agents. The Examiner cannot simply dismiss a scientific approach that is so widely used simply because the ultimate goal of the whole of the therapeutic discovery process is difficult to achieve.

In addition, Applicants have added claims 50-51 which recite "A method for identifying a **candidate** compound capable of treating a cellular growth or proliferation disorder..." Candidate therapeutic agents identified in an *in vitro* screen will naturally require further study and testing using other assays and ultimately clinical trials before it can be determined whether it is useful for treating cancer. This is not a reason to find that *in vitro* screening claims are not enabled. The value of in vitro screening using a specific target is based on the ability of such screening to narrow the group of compounds that are worthy of such further study and, as discussed previously, is a widely used scientific approach to identify candidate therapeutic agents for the treatment of cancer.

Third, the Examiner asserts that the claims are not enabled because "the specification fails to teach how to make a fragment of SEQ ID NO:2 or a protein 95% identical to SEQ ID NO:2 with a dehydrogenase activity ... [and] protein chemistry is unpredictable in the current state of art."

Applicants submit that the claims are fully enabled within the specification, as Applicants have provided teachings for every element needed for one of skill in the art to practice the claimed invention. Applicants have taught three domains within the DHDR-7 polypeptide which are conserved and essential for activity of the polypeptide, namely an acyl-CoA dehydrogenase middle domain, an acyl-CoA dehydrogenase C-terminal domain and an acyl-CoA dehydrogenase N-terminal domain or one large acyl-

CoA dehydrogenase domain comprising the three smaller domains (for example, refer to pages 10 and 11, beginning on line 32 of page 10, and figures 2A-D). Thus, Applicants have taught which regions of the polypeptide are amenable to alterations as well as those that are not amenable to alterations. In addition, the specification teaches how to generate functional variants of 95% identity by performing nucleotide substitutions leading to conservative amino acid substitutions within the polypeptide used in the claimed invention. As defined on page 21, "[c]onservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain." The Applicants have also defined which of the amino acids have similar side chains, thereby providing a skilled artisan the necessary tools to generate functional variants of the polypeptide of the invention. Applicants have also taught that biologically active fragments of the polypeptide used in the claimed invention may include sequences of 350 or greater amino acids (refer to pages 26-27 beginning at line 34 of page 26). For example, Applicants have provided a specific fragment having at least 350 amino acids of SEQ ID NO:2 comprising the acyl-CoA dehydrogenase domain located at about residues 85-438 of SEQ ID NO:2 (refer to page 84, lines 12-21 and figures 2C-D).

Further, Applicants have provided teachings for one of skill in the art to be able to perform assays to determine whether or not claimed sequences have the desired DHDR-7 activity. As taught on page12, lines 29-34 of the specification, such a DHDR-7 activity can include, for example, the modulation of " the dehydrogenation of acyl-CoA esters" and the modulation of "the beta oxidation cycle for fatty acids." As taught on page 7, lines 23-26 of the specification, DHDR-7 activity also includes, for example, the ability "to control cellular growth or proliferation disorders, e.g. cancer, including, but not limited to, colon cancer, breast cancer, lung cancer, and ovarian cancer." Based on these activities, one can perform assays on specific sequences to determine whether or not such sequences have the DHDR-7 activities. Such assays include, for example, assays that monitor " the alpha, beta-dehydrogenation of acyl-CoA esters, the reduction of flavoproteins, the beta oxidation of fatty acids, or the modulation of cellular proliferation, growth or differentiation" (refer to page 32, lines 3-13).

Therefore, Applicants have provided all the necessary information to enable one of skill in the art to 1) identify regions within the polypeptide used in the claimed invention that may be altered while maintaining activity; 2) generate fragments; and 3) perform assays to determine whether or not the sequences generated do in fact have the desired DHDR-7 activity.

Finally, the Examiner asserts that the claims were not enabled because "an acyl-CoA dehydrogenase...does not appear to be promiscuous in terms of its substrate...knowing the structural nature of the SEQ ID NO:2 substrate is also necessary to practice the invention but the specification does not provide any guidance on the structure of the substrate."

Applicants respectfully disagree with the Examiner's assertions regarding the teaching of Aoyama. Applicants submit that in fact, Aoyama supports the notion that acyl-CoA dehydrogenases are know to act upon a limited number of well known substrates, and determination of the substrate is well within the skill in the art to determine which substrate is applicable for assays upon the identification of a new acyl-CoA dehydrogenase. This was, in fact, the situation as exemplified in Aoyama, where they identified a novel family member, and subsequently the relevant substrate (see Aoyama pages 19088 and 19093-19094).

Furthermore, Applicants submit herewith a copy of Zhang et al. (Biochem. and Biophys. Comm. 2002, 297:1033-1042) to further evidence the substrate identification as routine. Zhang et al. have used this method to find that substrates for DHDR-7 (also known as ACAD-9, i.e. SEQ ID NO:2) are palmitoyl-coenzyme A and stearoyl-coenzyme A. Zhang et al. aligned ACAD-9 with the eight previously known members of the acyl-CoA dehydrogenase family. By comparing the amino acid residues at conserved positions, they found that residues critical for function and structure in medium- (MCAD) and very long-chain acyl-CoA dehydrogenases (VLCAD) were conserved in ACAD-9. Additionally, ACAD-9 has an extended C-terminal region similar to VLCAD. Assays showed that the substrates for VLCAD, palmitoyl-coenzyme A and stearoyl-coenzyme A, were indeed substrates for ACAD-9.

However, such a requirement is not in fact necessary in the present instance. Applicants respectfully direct the Examiner's attention to the recitation of the claimed methods. The methods recite the determination of binding of a compound to SEQ ID NO:2 and determination of ameliorating cellular growth or proliferation. In addition to acyl-CoA dehydrogenase activity, Applicants have described assaying the activity using cell based activity such as, but not limited to, cell growth and proliferation (see e.g., page 52, lines 3-13), a yeast two-hybrid assay (see e.g., page 55, lines 1-10), an immunoassay (see e.g., page 32-35, beginning on line 18 of page 32), and "determining the ability of a test compound to bind DHDR-7"(see e.g., page 51, lines 15-30).

In summary, for the reasons discussed, Applicants have satisfied the requirements for a full enabling disclosure for the presented claimed methods. In contrast to the Examiner's assertions, the ATCC deposit information and requirements have been met, as evidenced in the Preliminary Amendment and Statement of Biological Deposit filed herewith; and each and every element of the claimed methods has been sufficiently provided and/or is within the skill in the art.

Thus, Applicants submit that the scope of the present claims as presented herein, the teachings of the specification and the state of the art are sufficient to enable one of skill in the art to practice the invention without undue experimentation. Applicants thus respectfully submit the Examiner's rejection under 35 U.S.C. 112, first paragraph should be withdrawn. Such action is respectfully requested.

In view of the amendments and remarks herein, Applicants respectfully submit that the rejections presented by the Examiner are now overcome and that this application is in condition for allowance. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is believed that this paper is being filed timely and no additional extensions of time are required. In the event any additional extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Entry of the remarks made herein is respectfully requested.

Respectfully submitted,

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